Chemical Predictors of Wheeze among Farmer Pesticide Applicators in the Agricultural Health Study

JANE A. HOPPIN, DAVID M. UMBACH, STEPHANIE J. LONDON, MICHAEL C. R. ALAVANJA, and DALE P. SANDLER

Epidemiology Branch and Biostatistics Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina; and Occupational Epidemiology Branch, National Cancer Institute, National Institutes of Health, Rockville, Maryland

Pesticides may contribute to respiratory symptoms among farmers. Using the Agricultural Health Study, a large cohort of certified pesticide applicators in Iowa and North Carolina, we explored the association between wheeze and pesticide use in the past year. Self-administered questionnaires contained items on 40 currently used pesticides and pesticide application practices. A total of 20,468 applicators, ranging in age from 16 to 88 years, provided complete information; 19% reported wheezing in the past year. Logistic regression models controlling for age, state, smoking, and history of asthma or atopy were used to evaluate associations between individual pesticides and wheeze. Among pesticides suspected to contribute to wheeze, paraquat, three organophosphates (parathion, malathion, and chlorpyrifos), and one thiocarbamate (*S*-ethyl-dipropylthiocarbamate [EPTC]) had elevated odds ratios (OR). Parathion had the highest OR (1.5, 95% confidence interval [CI] 1.0, 2.2). Chlorpyrifos, EPTC, paraquat, and parathion demonstrated significant dose–response trends. The herbicides, atrazine and alachlor, but not 2,4-D, were associated with wheeze. Atrazine had a significant dose–response trend with participants applying atrazine more than 20 days/year having an OR of 1.5 (95% CI 1.2,1.9). Inclusion of crops and animals into these models did not significantly alter the observed OR. These associations, though small, suggest an independent role for specific pesticides in respiratory symptoms of farmers.

Keywords: wheeze; pesticides; organophosphates; paraquat; agricultural exposure

Farmers represent a high-risk group for occupational asthma and other respiratory diseases (1–7). Respiratory symptoms are more common among farmers and farm workers than other rural residents (1, 8–10). Agricultural workers have higher rates of long-term sick leave associated with respiratory disease than other workers (11).

Animals, grains, and dusts are the primary respiratory hazards associated with agriculture; however, a sparse literature suggests a role for pesticides. Insecticides, primarily cholinesterase-inhibiting compounds, may contribute to respiratory symptoms among agricultural workers (12, 13). Organophosphate insecticides have been associated with occupational asthma in case reports (14–16) and in a population-based survey of Saskatchewan farmers (8). Carbamate insecticide use was associated with self-reported asthma and lower mean values on lung function tests among Saskatchewan farmers (8). Residents exposed as a result of a chemical spill to metam sodium, a dithiocarbamate, exhibited persistent irritant-induced asthma (17). Insecticide application to livestock, but not to crops, was significantly associated with increased prevalence of wheeze among Iowa farmers (9); among Ohio grain farmers, mixing or applying pesticides was significantly associated with cough (18). Case reports suggest a link between fungicides and respiratory symptoms (19, 20). Fumigants, primarily methyl bromide and sulfur dioxide, can cause a severe acute pulmonary response in occupationally exposed subjects (21). Paraquat, an herbicide, is the only individual pesticide that has been studied with respect to respiratory disease in population-based settings. Paraquat was associated with increased wheeze among Nicaraguan banana workers (22) and decreased lung function among South African farm workers (23).

Previous studies of farmers and respiratory disease had limited ability to discriminate the potential effects of pesticide use and application from other contributors to respiratory symptoms owing to their relatively small sample sizes and the large number of exposures of interest. To better understand the role of pesticides on respiratory risk, we examined chemical use in the past year and self-reports of wheeze in the past year among the Agricultural Health Study (AHS) cohort. By using a large, heterogeneous cohort, we were able to control for other asthma-related risk factors and to explore the associations of individual pesticides with wheeze.

METHODS

The AHS is composed of certified pesticide applicators in Iowa and North Carolina (24). Approximately 52,000 farmers enrolled at pesticide certification by completing the enrollment questionnaire; 22,756 (44%) returned a second mailed questionnaire. Of eligible applicators, 82.4% enrolled in the study between 1994 and 1997. Applicators who did or did not return the second questionnaire were similar with regard to demographic characteristics, farming practices, and medical history (25). This analysis uses only subjects who returned both questionnaires.

The outcome, wheeze in the past year, was based on the question: "How many episodes of wheezing or whistling in your chest have you had in the past 12 months? No wheezing or whistling, 1–2 episodes, 3–6 episodes, 7–12 episodes, more than 12 episodes." Any positive response was included in the wheeze group. Information on other respiratory symptoms in the past year was not collected.

We assessed pesticide exposure and related activities using the questionnaire information. To evaluate exposures temporally relevant for the wheeze outcome, we limited analysis to the 40 pesticides used in the past year. Besides the individual chemicals, we created summary variables for three classes of pesticides of *a priori* interest (organophosphates, carbamates, and thiocarbamates). The organophosphate class contained chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, and trichlorfon. The carbamate class contained aldicarb, benomyl, carbofuran, and carbaryl. The thiocarbamate class contained butylate, S-ethyl-dipropylthiocarbamate (EPTC), maneb, and ziram. To evaluate overall annual pesticide usage, we calculated summary variables for: (*1*) total pesticide use, (*2*) total pesticide use within each pesticide type (e.g., herbicide, insecticide), and (*3*) total pesticide use within each class of *a priori* interest. Frequency of application was reported as < 5, 5–9, 10–19, 20–39, 40–59, 60–150, and > 150 days for herbicides and insecticides. We calculated total days using the category midpoints, except for the top category where we used 150% of the lower boundary.

(*Received in original form June 18, 2001; accepted in final form October 26, 2001*)

Supported by intramural research funds of the National Cancer Institute and the National Institute of Environmental Health Sciences.

Correspondence and requests for reprints should be addressed to Jane A. Hoppin, Sc.D., NIEHS, Epidemiology Branch, MD A3-05, PO Box 12233, Research Triangle Park, NC 27709-2233. E-mail: hoppin1@niehs.nih.gov

Am J Respir Crit Care Med Vol 165. pp 683–689, 2002
DOI: 10.1164/rccm.2106074
Internet address: www.atsjournals.org

TABLE 1. DEMOGRAPHIC AND MEDICAL CHARACTERISTICS OF FARMER PESTICIDE APPLICATORS IN THE AHS BY WHEEZE STATUS

	All Participants (*n = 20,468*)		
	Wheeze (*n = 3,838*)	No Wheeze (*n = 16,630*)	p Value*
Age, yr			
mean, SD	48 (13.3)	49 (13.0)	
median, range	47 (16–87)	48 (16–88)	
Race			
White	98%	98%	NS
Other	2%	2%	
Sex			
Female	2%	2%	NS
Male	98%	98%	
State			
Iowa	63%	69%	
North Carolina	37%	31%	< 0.01
Smoking			
Never	44%	57%	
Past	33%	33%	< 0.01‡
Current	24%	10%	< 0.01‡
Asthma	18%	2%	< 0.01
Atopy†	21%	9%	< 0.01
Lifetime years of pesticide application			0.49
< 1 yr	2%	2%	
2–5 yr	10%	10%	
6–10 yr	14%	14%	
11–20 yr	32%	33%	
21–30 yr	26%	25%	
> 30 yr	16%	15%	

Definition of abbreviation: NS = not significant.
* P value for chi-square test.
† Atopy defined as self-report of hay fever or eczema.
‡ Compared with never-smokers.

Exposures were evaluated using a base logistic regression model controlling for age, state, smoking history (current, past, never), and asthma–atopy status. Atopy history was defined as a self-report of a diagnosis of either eczema or hay fever. The association of chemical-specific exposures with wheeze was evaluated in two ways: ever/never use in the past year and dose–response modeling using application frequency categories. Each pesticide was added to the base model individually. For chemical-specific analyses, subjects were excluded if they reported using the chemical ever but not in the past year. Dose–response modeling was limited to insecticides and herbicides. To address potential confounding by multiple exposures, we constructed models that included chemicals commonly applied together (26) and chemical application methods used. We also constructed models that included pesticides with associated crops or animals. We used interaction models to evaluate whether atopic or asthmatic subjects responded differently to exposure. For total number of days of pesticide application in the last year, dose–response models used the base model and evaluated exposure based on the questionnaire categories for the individual pesticide types. For pesticide application methods, users of each method were compared with a referent group who did not apply pesticides of that type. All statistical analysis was performed using SAS (Cary, NC).

RESULTS

A total of 20,468 farmer applicators (90% of eligible subjects) had complete information on all covariates of interest. Subjects were predominantly white males; they ranged in age from 16 to 88 years at the time of enrollment (Table 1). Nineteen percent of subjects reported at least one episode of wheeze in the year before enrollment. Five percent reported a doctor diagnosis of asthma with 54% of these individuals diagnosed before age 20; 11% had a history of eczema or hay fever, our atopy definition. As expected, subjects who wheezed were more likely to have a history of asthma and atopy. North Carolina residents were more likely to report wheeze than their Iowa counterparts ($p < 0.01$). Both current and former smokers were more likely to report wheeze in the past year. Shortness of breath when hurrying was reported more often by subjects who reported wheeze in the past year (51% versus 19%). The total years of pesticide application did not differ between subjects who reported wheeze and those who did not.

Information was available on 40 pesticides applied and crops and animals raised in the year before enrollment. The exposure prevalences and the adjusted odds ratios (OR) for use of each chemical are presented in Table 2. The results of trend tests for each herbicide and insecticide are also included. Eleven of the 40 pesticides (27%) were significantly associated with wheeze when evaluated for ever use; of these, all 10 for which we constructed dose–response models had significant tests for trend ($p < 0.05$). Dose–response models were not constructed for fungicides and fumigants because of the limited number of application days. Dose–response models for six chemicals are presented in Table 3. Chemicals were selected for presentation on the basis of volume of use and *a priori* interest; dose–response models for all chemicals are available from the authors. When chemicals commonly applied together and crop and animal-related exposures were included in the same model, the results were essentially the same as those reported in Tables 2 and 3.

Interaction models were used to explore whether atopic or asthmatic subjects had different odds of wheeze with exposure than could be explained by the chemical alone. Three chemicals, butylate, fonofos, and malathion had significant interactions ($p < 0.05$) with atopy. Atopic subjects who used butylate ($p_{interaction} = 0.02$) or fonofos ($p_{interaction} = 0.04$) in the past year were much more likely to wheeze than atopic subjects who did not use these chemicals; conversely, atopic subjects who used malathion were less likely to wheeze ($p_{interaction} = 0.01$). Among asthmatic subjects, five chemicals (benomyl, coumaphos, glyphosate, paraquat, and permethrin [poultry]) showed a significantly lower odds of wheeze. When chemical use on animals was added to the models for coumaphos and permethrin, the interaction was still significant but the OR for wheeze among nonasthmatics was attenuated toward the null. For paraquat, a chemical not associated with animal exposure, the OR for wheeze among nonasthmatics was 3.3 (95% confidence interval [CI] = 1.4, 7.6). In interaction models, the OR for wheeze among nonasthmatics were 2.9 (95% CI = 1.1, 8.1) for benomyl and 1.5 (95% CI = 1.1, 2.1) for glyphosate.

Farmers applied between 0 and 23 pesticides in the year before enrollment, with a median of three. Only a small portion of our population applied fungicides and fumigants (16% for fungicides and 4% for fumigants). Total pesticide usage was significantly associated with odds of wheeze in categorical dose–response models adjusted for covariates included in the base models (Table 4).

Activities related to pesticide application may also contribute to respiratory symptoms. We evaluated three aspects: personal protective equipment, solvents as additives, and pesticide application methods. Eleven types of personal protective gear, including respirators, dust masks, and chemically resistant gloves were evaluated; none was associated with wheeze, either positively or negatively (data not shown). Nine percent of subjects reported using solvents as additives to pesticides. Subjects who reported using solvent additives had an OR for wheeze of 1.3 (95% CI = 1.1, 1.5). OR for wheeze associated with each crop application method, stratified by pesticide type are shown in Figure 1. The referent group for application methods was those individuals who did not report applying

TABLE 2. CHEMICAL-SPECIFIC ODDS RATIO FOR WHEEZE IN THE PAST YEAR AMONG FARMER PESTICIDE APPLICATORS IN THE AHS COHORT, 1994–1997

Chemical	Wheeze (*n* = 3,838) % exposed	No Wheeze (*n* = 16,630) % exposed	Adjusted OR*	95% CI	p Trend†	Number of Levels‡
Herbicides						
2,4-D	62.4	64.7	0.99	(0.88, 1.11)	0.46	6
Alachlor	21	17.6	1.24	(1.09, 1.42)	< 0.01	5
Altrazine	54.6	53.2	1.20	(1.07, 1.34)	< 0.01	5
Butylate	1.6	1.2	1.23	(0.86, 1.77)	0.29	3
Chlorimuron ethyl	16.4	14.5	1.14	(1.02, 1.29)	< 0.01	4
Cyanazine	15.5	15.8	1.03	(0.90, 1.18)	0.17	5
Dicamba	30.8	32.3	1.06	(0.95, 1.19)	0.22	5
EPTC	4	3.4	1.32	(1.05, 1.65)	0.01	4
Glyphosate	68.1	64.9	1.05	(0.95, 1.17)	0.04	6
Imazethapyr	34.2	35.8	1.06	(0.95, 1.17)	0.02	5
Metolachlor	27.4	27	1.07	(0.97, 1.19)	0.26	5
Metribuzin	6.7	6.4	1.13	(0.94, 1.37)	0.03	4
Paraquat	5	3.6	1.27	(1.04, 1.56)	< 0.01	4
Pendimethalin	18.3	17	1.04	(0.93, 1.17)	0.05	5
Petroleum oil	10.3	7.9	1.28	(1.11, 1.48)	< 0.01	5
Trifluralin	29.3	28.3	1.12	(1.00, 1.25)	0.03	5
Insecticides						
Organophosphates						
Chlorpyrifos	24.2	22	1.12	(1.01, 1.25)	0.01	5
Coumaphos	3.5	3.1	0.95	(0.75, 1.20)	0.63	4
Diazinon	8	6.1	1.04	(0.88, 1.23)	0.52	4
Dichlorvos	3.2	3	1.14	(0.90, 1.44)	0.30	4
Fonofos	5.4	5.3	1.08	(0.89, 1.31)	0.38	4
Malathion	34.7	30.7	1.14	(1.02, 1.28)	0.01	5
Parathion	1.4	0.8	1.50	(1.04, 2.16)	0.01	3
Phorate	3.8	3.5	1.06	(0.84, 1.34)	0.72	4
Terbufos	16.8	16.7	1.09	(0.96, 1.23)	0.21	5
Trichlorfon	0.2	0.1	1.93	(0.69, 5.41)	—	
Carbamates						
Aldicarb	3.8	3.1	0.97	(0.78, 1.20)	0.89	4
Carbaryl	20.1	16.3	1.13	(0.98, 1.30)	0.01	5
Carbofuran	3.6	3.2	1.11	(0.86, 1.42)	0.51	3
Other insecticides						
Lindane	1.4	1.5	0.82	(0.58, 1.16)	0.80	3
Permethrin (crops)	6.4	5	1.13	(0.95, 1.35)	0.07	4
Permethrin (poultry)	5.8	5.1	1.26	(1.06, 1.51)	< 0.01	4
Fungicides						
Benomyl (also carbamate)	2.4	2	1.03	(0.79, 1.35)	NA§	NA
Captan	7.2	6.7	1.01	(0.86, 1.19)	NA	NA
Chlorothalonil	4	3.5	0.93	(0.75, 1.16)	NA	NA
Maneb	3	2.3	1.16	(0.91, 1.48)	NA	NA
Metalaxyl	11	7.8	1.19	(1.02, 1.38)	NA	NA
Ziram	0.3	0.2	1.02	(0.48, 2.16)	NA	NA
Fumigants						
Aluminum phosphide	0.5	0.6	0.67	(0.39, 1.18)	NA	NA
Brom_O_Gas	5.7	4.2	1.11	(0.90, 1.35)	NA	NA

* Odds ratios adjusted for age, state, past smoking, current smoking, and asthma/atopy. Comparison group is those who never reported using the pesticide.

† Trend test using questionnaire categories.

‡ Number of levels, possible categories (never used, < 5, 5–9, 10–19, 20–39 d, ⩾ 40 d/yr). The higher levels were collapsed as required to obtain at least 1% in each cell.

§ NA = not applicable: trend test not performed for fumigants and fungicides, owing to the few days of usage/year.

chemicals in that pesticide type. The OR for each application method appear similar regardless of pesticide class, with the possible exception of air-blast application for fungicides. The adjusted ORs for application of insecticides to animals are presented in Table 5. When animal exposure was added into these models, there was little attenuation of these ORs.

DISCUSSION

Farming involves multiple exposures, many of which may contribute to respiratory symptoms and disease. With the advantage of the large sample size of the AHS and the heterogeneity of farming practices among farmers in Iowa and North Carolina, we were able to control for multiple exposures to identify pesticides associated with increased odds of wheeze. Our results complement and extend other work regarding pesticides and respiratory symptoms among agricultural workers. Prevalence of wheeze was associated with individual pesticides independent of animals, crops, and grains. Wheeze was also associated with total days of chemical application. Twenty-seven percent of the pesticides evaluated were significantly associated with wheeze, most in a dose-dependent manner. The pesticides associated with self-reported wheeze are consistent with available epidemiologic and toxicologic data.

Organophosphate and carbamate compounds are thought to contribute to respiratory symptoms through cholinesterase

TABLE 3. SELECTED CATEGORICAL DOSE–RESPONSE MODELS FOR WHEEZE AMONG FARMER PESTICIDE APPLICATORS IN THE AHS, 1994–1997

Pesticide	Wheeze (*n* = 3,838) % exposed	No Wheeze (*n* = 16,630) % exposed	OR*	95% CI
2,4-D				
Never used	38	36	1.00	
< 5 d	21	23	0.96	(0.83, 1.11)
5–9 d	20	21	0.98	(0.85, 1.14)
10–19 d	13	13	1.03	(0.87, 1.22)
20–39 d	6	5	1.03	(0.81, 1.31)
⩾ 40 d	2	1	1.25	(0.83, 1.90)
Atrazine				
Never used	46	47	1.00	
< 5 d	17	18	1.12	(0.96, 1.29)
5–9 d	19	19	1.17	(1.01, 1.36)
10–19 d	13	11	1.27	(1.08, 1.51)
⩾ 20 d	6	4	1.53	(1.21, 1.95)
Chlorpyrifos				
Never used	76	78	1.00	
< 5 d	9	9	1.01	(0.86, 1.18)
5–9 d	9	7	1.33	(1.13, 1.57)
10–19 d	4	4	0.91	(0.71, 1.15)
⩾ 20 d	2	1	1.61	(1.12, 2.31)
EPTC				
Never used	96	97	1.00	
< 5 d	1	1	1.14	(0.79, 1.63)
5–9 d	2	1	1.44	(0.99, 2.08)
⩾ 10 d	1	1	1.47	(0.95, 2.28)
Parathion				
Never used	99	99	1.00	
< 5 d	0.4	0.3	1.32	(0.69, 2.51)
⩾ 5 d	1	1	1.72	(1.10, 2.68)
Paraquat				
Never used	95	96	1.00	
< 5 d	2	2	1.33	(0.99, 1.78)
5–9 d	1	1	1.12	(0.77, 1.61)
⩾ 10 d	2	1	1.31	(0.92, 1.86)

* Odds ratios adjusted for age, state, past smoking, current smoking, and asthma/atopy.

Control group includes only those who never used the pesticide. Exposed group contains only those who used pesticide last year.

inhibition, which may promote bronchoconstriction (8, 14). Among Saskatchewan grain farmers, Senthilselvan and colleagues (8) observed significant associations between asthma and use of cholinesterase-inhibiting pesticides, defined as phosphodithioates (OR = 1.5, 95% CI 1.0, 2.4) and carbamates (OR = 1.9, 95% CI = 1.2, 3.0). In our data, parathion, malathion, and chlorpyrifos were each individually associated with wheeze in a dose-dependent manner. Parathion is one of the most potent organophosphate insecticides, and thus, its strong association with wheeze is consistent with a role of cholinesterase inhibitors. We saw no association with individual carbamates or thiocarbamates with the exception of EPTC and carbaryl, which were related to wheeze in a dose-dependent fashion.

Paraquat exposure at high doses causes pulmonary fibrosis in humans and animals independent of exposure route (27). A variety of respiratory effects have been observed among occupationally exposed subjects. On South African fruit farms, long-term exposure to paraquat was significantly associated with arterial oxygen saturation in a dose-dependent manner, though there were no differences with regard to respiratory symptoms, spirometry, gas transfer, and chest radiography (23). Among Nicaraguan banana workers, a threefold increase in wheeze and shortness of breath was associated with more intense paraquat exposure; there was no increased prevalence of wheeze at lower levels of paraquat exposure (22). Among our subjects, paraquat was significantly associated with wheeze in a dose-dependent fashion. Although the mechanism of action of paraquat for less severe respiratory symptoms, such as cough and wheeze, is not known, paraquat is a known skin irritant and may also irritate the mucosal surface of the lung (21).

In addition to paraquat and EPTC, we saw significant dose–response associations with other herbicides, including atrazine and alachlor; these associations were independent of corn and other grain exposures. Wheeze was not associated with 2,4-D, the most commonly applied herbicide. Total days of herbicide application were significantly associated with wheeze. However, most of the increased prevalence of wheeze was observed among individuals who applied herbicides more than 150 days per year (OR = 1.6, 95% CI = 1.2, 2.1); ∼ 4% of the farmers in this study applied herbicides at that rate. Previous studies among Saskatchewan farmers (8) and Iowa farmers (9) did not observe respiratory symptoms associated with herbicide use.

Insecticide use on animals has been associated with wheeze among farmers in Iowa (9). Permethrin, a pyrethroid, was the only insecticide reported separately for crop and animal use in our data. Its use on poultry was associated with wheeze, but use on crops was not. For other insecticides that may be used on animals, we saw no significant association of wheeze with coumaphos and dichlorvos, whereas we observed an increased odds of wheeze among chlorpyrifos and malathion applicators. All animal application methods, except rope wick, were significantly associated with wheeze (Table 5). Although our data do not allow us to directly link the chemical, the application method, and the animal (or crop) to which the chemical was applied, our results suggest both chemical-specific and application method–specific contributions to wheeze prevalence among farmer applicators independent of animal exposure. However, our measure of animal exposure may be too crude (e.g., raised in the past year) and may represent a surrogate for other animal-related exposures.

When considering multiple exposures, we chose to evaluate only those for which we had some evidence that they were used in combination at the same time. Given the large sample size and the large number of potential covariates, the number of possible combinations is great. The literature on the role of specific pesticides and respiratory symptoms is sparse, although there are data suggesting associations. For this exploratory analysis, we evaluated all chemicals for which we had sufficient data. In addition, we had sufficient power to assess whether response to chemical exposure was different among atopics and asthmatics. These analyses suggested that atopics may have a different response to exposure for benomyl, fonofos, and malathion. The interactions for asthmatics suggested a lower response to the chemicals among asthmatics; whether this indicates that asthmatics are less influenced by chemical exposure or that sensitive asthmatics avoid chemical exposures cannot be determined by this evaluation. We have no information on asthma severity or medication use to evaluate this in our data. However, the odds of wheeze of particular pesticides (paraquat, benomyl, glyphosate) were greater among nonasthmatics, suggesting a higher risk group to explore in future studies.

We had information on chemical use in the past year and crops and animals raised in the past year; however, we did not have detailed information regarding the use of specific pesticides on individual crops and animals. Information regarding pesticide formulation (e.g., granular, emulsifiable concentrate), pesticides premixed together, and specific solvents or other additives used was not available. Although we observed significant results with individual pesticides in a dose-dependent

TABLE 4. DOSE–RESPONSE MODELS FOR TOTAL PESTICIDE USAGE AND WHEEZE AMONG FARMER PESTICIDE APPLICATORS IN THE AHS, 1994–1997

Chemical days per year*†	Wheeze (*n = 3,838*) % exposed	No Wheeze (*n = 16,630*) % exposed	OR‡	95% CI	p Trend
Total pesticides					< 0.01
Did not mix/apply last year	21	21	1.00		
< 5 d	7	8	0.94	(0.81, 1.11)	
5–9 d	9	10	0.96	(0.83, 1.11)	
10–19 d	14	16	0.96	(0.84, 1.08)	
20–39 d	20	20	1.02	(0.91, 1.15)	
40–59 d	10	10	1.05	(0.91, 1.21)	
60–150 d	14	12	1.19	(1.04, 1.36)	
> 150 d	5	3	1.42	(1.16, 1.74)	
Total insecticides					< 0.01
Didn't mix/apply last year	49	51	1.00		
< 5 d	12	14	0.90	(0.80, 1.02)	
5–9 d	13	13	1.07	(0.95, 1.20)	
10–19 d	12	11	1.00	(0.89, 1.14)	
20–39 d	8	7	1.11	(0.96, 1.29)	
40–59 d	3	2	1.17	(0.92, 1.49)	
⩾ 60 d	4	2	1.55	(1.25, 1.93)	
Total herbicides					< 0.01
Didn't mix/apply last year	23	23	1.00		
< 5 d	10	10	1.03	(0.89, 1.20)	
5–9 d	11	13	0.95	(0.82, 1.09)	
10–19 d	16	17	1.03	(0.91, 1.17)	
20–39 d	19	19	1.08	(0.96, 1.22)	
40–59 d	10	9	1.20	(1.02, 1.40)	
60–150 d	9	8	1.21	(1.03, 1.42)	
> 150 d	3	2	1.58	(1.21, 2.08)	
Specific chemical classes§					
Organophosphates					0.1
Didn't mix/apply last year	56	58	1.00		
< 5 d	3	3	1.06	(0.85, 1.33)	
5–9 d	23	24	1.02	(0.93, 1.11)	
10–19 d	12	11	1.09	(0.97, 1.23)	
⩾ 20 d	6	5	1.14	(0.96, 1.35)	
Carbamates					0.3
Didn't mix/apply last year	79	82	1.00		
< 5 d	9	9	0.95	(0.83, 1.09)	
5–9 d	5	4	1.04	(0.86, 1.25)	
10–19 d	4	3	1.01	(0.83, 1.23)	
⩾ 20 d	3	2	1.21	(0.97, 1.52)	

* Questionnaire cutpoints were used where sample sizes were > 1% per cell.
† Obtained by summing over all the chemicals in that category used in the past year.
‡ Odds ratios adjusted for age, state, past smoking, current smoking, and asthma/atopy.
§ Thiocarbamates were not presented because different pesticide types used different questionnaire cutpoints.

fashion, the observed OR may be a result of some other aspect of the technical product, such as the so-called inert ingredients. Access to these proprietary data would allow us to explore this aspect of potential confounding. The observed OR reflect the applicators' exposure to the technical products and not just the active ingredients. This may explain discrepancies between the toxicology data on the active ingredients, which offer limited evidence of effects, and the epidemiologic data which suggest associations.

Wheeze and asthma are common respiratory concerns among farmers worldwide. Our population reported prevalences of asthma (5%) and wheeze (19%) that were consistent with those observed in other populations. Data regarding the prevalence of asthma among farmers are limited (4); the reported prevalence of asthma among farmers ranges from 6% in rural Saskatchewan (10) to 12% current asthma among New Zealand farmers (28). The prevalence of current wheeze among Ohio grain farmers was 8% (18), 10% among Iowa farmers (9), and 27% among Saskatchewan farmers (1).

The healthy population may bias our results toward the null and thus, contribute to the low OR observed. Respiratory morbidity among farmers influences their ability to farm (29) and may determine the chemicals that they use and the crops and animals that they raise. Because farming is a lifelong occupation, those subjects who have extreme respiratory disease are likely to remove themselves from farming and to limit exposures that exacerbate respiratory symptoms. In the Netherlands, a selection effect was observed among grain processing workers based on decline in lung function, with the most impaired workers more likely to leave the industry than those with less rapid decline in lung function (30). Among Dutch pig farmers, a lower prevalence of childhood asthma and atopy was regarded as a health-based selection process that would reduce the impact of work-related respiratory symptoms (31). A similar selection process may be expected among our farmers. The observed interactions with asthma and specific pesticides are consistent with this. The detection of significant associations among a self-selected population is relevant for application of these results to other populations, especially those who may be sensitive because of age or disease status.

The AHS was initially designed to look at cancer risk among farmers and their families. During questionnaire development,

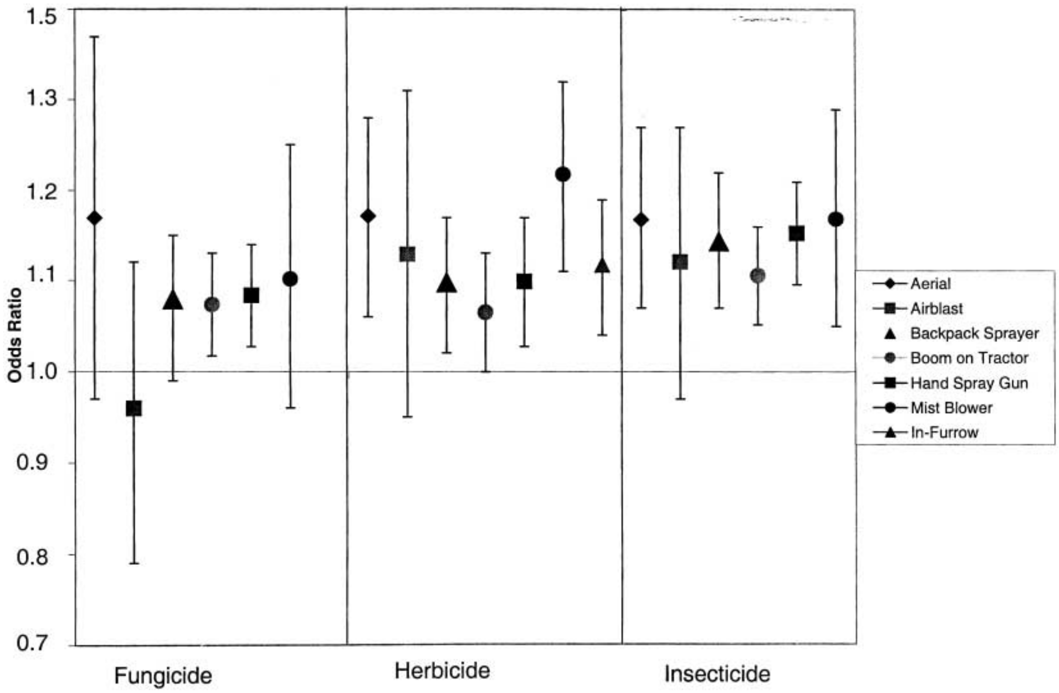

Figure 1. Odds ratios for seven pesticide application methods and wheeze, stratified by pesticide type.

information on other health outcomes of interest was added, but with limited information on respiratory symptoms. Thus, we limited this analysis to wheeze and chemical use in the past year. Future queries of our cohort will contain more information regarding respiratory symptoms and disease. However, as an initial analysis, wheeze and asthma are appropriate self-reported metrics. Other investigators (8) have demonstrated among farmers that self-reported asthmatic subjects have a higher symptom prevalence and lower lung function tests than nonasthmatics. In our study, subjects who wheeze were also more likely to report having shortness of breath while hurrying (51% versus 19%). The questionnaire asked about numerous pesticides and a wide variety of health outcomes, although possible, it is unlikely that our results are due to overreporting among wheezing subjects. Farmers have been demonstrated to be accurate reporters of pesticide application because of their dual roles as owners and operators, which give them complete information regarding exposure (32). Our subjects are all licensed pesticides applicators; they have an interest in keeping chemicals on the market and are unlikely to selectively report responses.

Unlike other studies, we had sufficient power to explore the associations of individual chemicals with wheeze while controlling for other farming-related exposures. This study is the first to include farmers from the southern United States who grow a different variety of crops and are impacted by different pests than farmers in other regions of the United States. We saw associations with specific pesticides, primarily organophosphates and paraquat, though total application days of all insecticides and herbicides were significantly associated with wheeze as well. Application of insecticides to animals was significantly associated with wheeze. The observed ORs were small and residual confounding may explain these associations; however, given the healthy population, the infrequent exposures, and the consistency with the toxicology and epidemiology literature, these results suggest a role for pesticides in relation to respiratory symptoms among farmers in the AHS.

TABLE 5. ANIMAL INSECTICIDE APPLICATION METHODS AND ODDS OF WHEEZE IN THE PAST YEAR AMONG FARMER PESTICIDE APPLICATORS IN THE AHS COHORT, 1994–1997

Pesticide Application Method*	Wheeze (*n* = *3,838*) % exposed†	No Wheeze (*n* = *16,630*) % exposed†	OR‡	95% CI
Do not apply livestock insecticides	47	49	1.00	
Dip animals	3	2	1.52	(1.23, 1.89)
Dust animals	14	11	1.29	(1.15, 1.45)
Ear tag	18	15	1.25	(1.12, 1.39)
Fog/mist animals	9	6	1.64	(1.42, 1.90)
Hang pest strips in barn	6	4	1.43	(1.21, 1.69)
Pour on animals	28	26	1.19	(1.08, 1.30)
Rope wick	5	5	1.07	(0.90, 1.27)
Spray animals	32	30	1.21	(1.11, 1.33)
Spray buildings	20	17	1.31	(1.18, 1.45)
Other livestock insecticide methods	2	1	1.34	(1.00, 1.80)

* Methods are not mutally exclusive. Individuals may use more than one application method within a pesticide group.
† Percentage in cohort. Odds ratio is based on exclusion of subjects who used other animal application methods.
‡ Odds ratios adjusted for age, state, past smoking, current smoking, and asthma/atopy.

Acknowledgment: The authors thank Stuart Long for data analysis and Donna Baird for questionnaire development. This work could not have been completed without the hard work of the Iowa and North Carolina Field Stations and their project staff, Nyla Logsden-Sackett, Chuck Lynch, Joy Pierce, and Margaret Pennybacker.

References

1. Dosman JA, Graham BL, Hall D, Van Loon P, Bhasin P, Froh F. Respiratory symptoms and pulmonary function in farmers. *J Occup Med* 1987;29:38–43.
2. Fishwick D, Pearce N, D'Souza W, Lewis S, Town I, Armstrong R, Kogevinas M, Crane J. Occupational asthma in New Zealanders: a population based study. *Occup Environ Med* 1997;54:301–306.
3. Schenker M, Ferguson T, Gamsky T. Respiratory risks associated with agriculture. *Occup Med State of Art Rev* 1991;6:415–428.
4. Schenker MB, Christiani D, Cormier Y, Dimich-Ward H, Doekes G, Dosman J, Douwes J, Dowling K, Enarson D, Green F, *et al.* Respiratory health hazards in agriculture. *Am J Respir Crit Care Med* 1998; 158:S1–S76.
5. Schwartz DA. Etiology and pathogenesis of airway disease in children and adults from rural communities. *Environ Health Perspect* 1999;107: 393–401.
6. Melbostad E, Eduard W, Magnus P. Determinants of asthma in a farming population. *Scand J Work Environ Health* 1998;24:262–269.
7. Karjalainen A, Kurppa K, Virtanen S, Keskinen H, Nordman H. Incidence of occupational asthma by occupation and industry in Finland. *Am J Ind Med* 2000;37:451–458.
8. Senthilselvan A, McDuffie HH, Dosman JA. Association of asthma with use of pesticides: results of a cross-sectional survey of farmers. *Am Rev Respir Dis* 1992;146:884–887.
9. Sprince NL, Lewis MQ, Whitten PS, Reynolds SJ, Zwerling C. Respiratory symptoms: associations with pesticides, silos, and animal confinement in the Iowa Farm Family Health and Hazard Surveillance Project. *Am J Ind Med* 2000;38:455–462.
10. Masley ML, Semchuk KM, Senthilselvan A, McDuffie HH, Hanke P, Dosman JA, Cessna AJ, Crossley MF, Irvine DG, Rosenberg AM, *et al.* Health and environment of rural families: Results of a community canvass survey in the Prairie Ecosystem Study (PECOS). *J Agric Saf Health* 2000;6:103–115.
11. Nathell L, Malmberg P, Lundback B, Nygren A. Impact of occupation on respiratory disease. *Scand J Work Environ Health* 2000;26:382–389.
12. Yemaneberhan H, Bekele Z, Venn A, Lewis S, Parry E, Britton J. Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. *Lancet* 1997;350:85–90.
13. Ohayo-Mitoko GJA, Kromhout H, Simwa JM, Boleij JSM, Heederik D. Self reported symptoms and inhibition of acetylcholinesterase activity among Kenyan agricultural workers. *Occup Environ Med* 2000;57: 195–200.
14. Weiner A. Bronchial asthma due to the organic phosphate insecticides. *Ann Allergy* 1961;19:397–401.
15. Bryant DH. Asthma due to insecticide sensitivity. *Aust NZ J Med* 1985;15:66–68.
16. Deschamps D, Questel F, Baud FJ, Gervais P, Dally S. Persistent asthma after acute inhalation of organophosphate insecticide. *Lancet* 1994; 344:1712.
17. Cone JE, Wugofski L, Balmes JR, Das R, Bowler R, Alexeeff G, Shusterman D. Persistent respiratory health effects after a metam sodium pesticide spill. *Chest* 1994;106:500–508.
18. Wilkins JR, Engelhardt HL, Rublaitus SM, Crawford JM, Fisher JL, Bean TL. Prevalence of chronic respiratory symptoms among Ohio cash grain farmers. *Am J Ind Med* 1999;35:150–163.
19. Royce S, Wald P, Sheppard D, Balmes J. Occupational asthma in a pesticides manufacturing worker. *Chest* 1993;103:295–296.
20. Honda I, Kohrogi H, Ando M, Araki S, Ueno T, Futatsuka M, Ueda A. Occupational asthma induced by the fungicide tetrachloroisophthalonitrile. *Thorax* 1992;47:760–761.
21. Popendorf W, Donham KJ, Easton DN, Silk J. A synopsis of agricultural respiratory hazards. *Am Ind Hyg Assoc J* 1985;46:154–161.
22. Castro-Gutierrez N, McConnell R, Andersson K, Pacheco-Anton F, Hogstedt C. Respiratory symptoms, spirometry and chronic occupational paraquat exposure. *Scand J Work Environ Health* 1997;23:421–427.
23. Dalvie MA, White N, Raine R, Myers JE, London L, Thompson M, Christiani DC. Long-term respiratory health effects of the herbicide, paraquat, among workers in the Western Cape. *Occup Environ Med* 1999;56:391–396.
24. Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, Pennybacker M, Rothman N, Dosemeci M, Bond AE, *et al.* The Agricultural Health Study. *Environ Health Perspect* 1996;104:362–369.
25. Tarone RE, Alavanja MC, Zahm SH, Lubin JH, Sandler DP, McMaster SB, Rothman N, Blair A. The Agricultural Health Study: factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. *Am J Ind Med* 1997;31:233–242.
26. Crop Protection Reference, 11th edition. New York: Chemical and Pharmaceutical Press; 1995.
27. Honore P, Hantson P, Fauville JP, Peeters A, Manieu P. Paraquat poisoning. "State of the art." *Acta Clin Belg* 1994;49:220–228.
28. Kimbell-Dunn M, Bradshaw L, Slater T, Erkinjuntti-Pekkanen R, Fishwick D, Pearce N. Asthma and allergy in New Zealand farmers. *Am J Ind Med* 1999;35:51–57.
29. Tupi K, Vohlonen I, Terho EO, Husman K. Effects of respiratory morbidity on occupational activity among farmers. *Eur J Respir Dis Suppl* 1987;152:206–211.
30. Post W, Heederik D, Houba R. Decline in lung function related to exposure and selection processes among workers in the grain processing and animal feed industry. *Occup Environ Med* 1998;55:349–355.
31. Vogelzang PF, van der Gulden JW, Tielen MJ, Folgering H, van Schayck CP. Health-based selection for asthma, but not for chronic bronchitis, in pig farmers: an evidence-based hypothesis. *Eur Respir J* 1999;13:187–189.
32. Blair A, Zahm SH. Patterns of pesticide use among farmers: implications for epidemiologic research. *Epidemiology* 1993;4:55–62.